Investigators identify potential new targets to overcome treatment resistance in aggressive breast cancer

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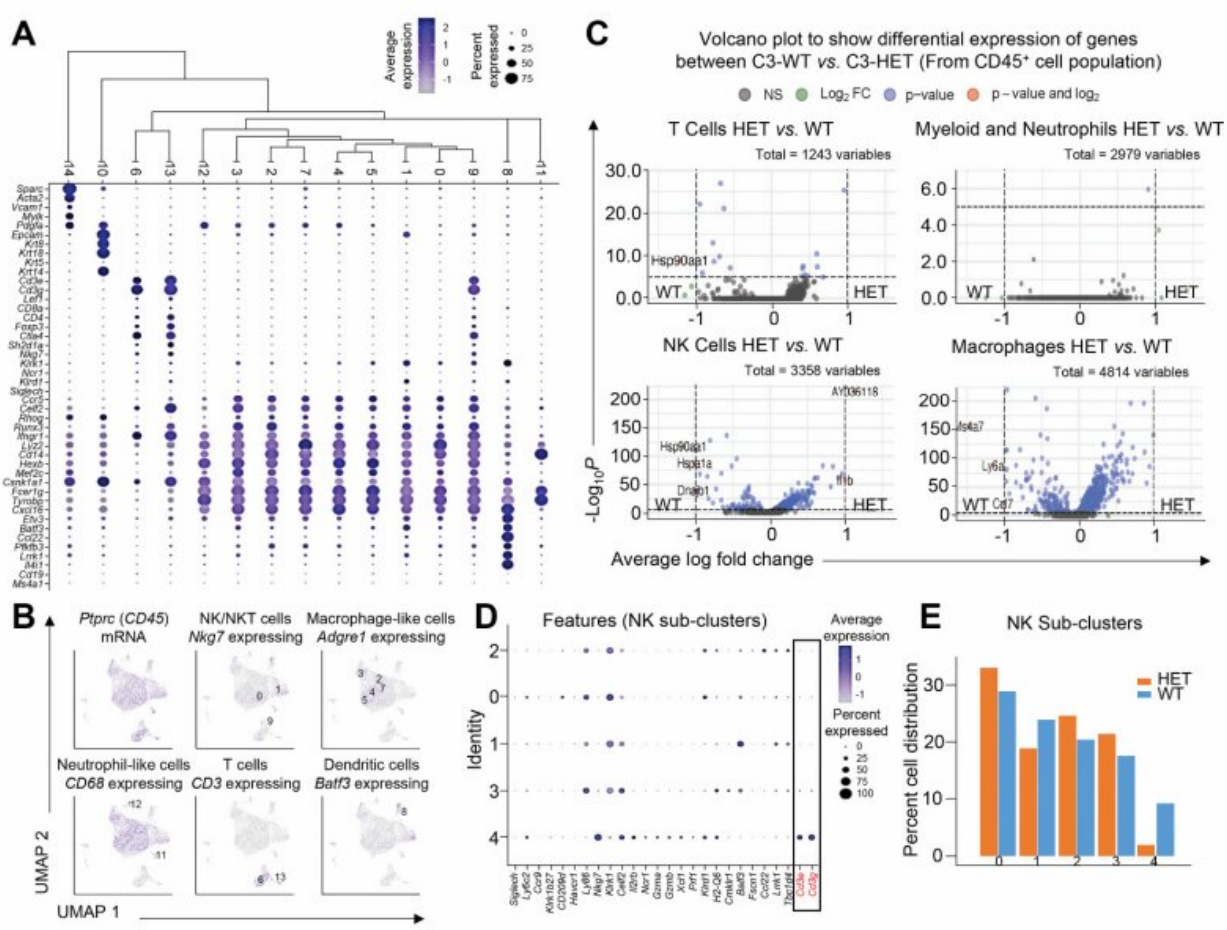

NK cell heterogeneity was assessed by single cell-RNA sequencing in C3-HET tumors. (A) Expression of genes utilized to define population of all clusters of CD45^{+} cells. (B) Feature plots showing expression of CD45 mRNA and genes used to identify NK cells and NKT cells (Nkg7), Macrophage-like cells

(Adgre1), Neutrophil-like cells (CD68), T cells (CD3) and dendritic cells (Batf3). (C) Volcano plots showing differentially expressed genes between C3-WT and C3-HET T cells, Myeloid cells and neutrophils, NK cells, and macrophages. (D) Expression of genes across C3-WT and C3-HET NK population to define sub-clusters of NK cells. Higher expression of red highlighted gene Cd3e and Cd3g only in sub-cluster 4 indicated its composition mainly as NKT cells. (E) Bar graph depicts the number of cells within each NK sub-cluster (0-4) as a percentage in C3-WT and C3-HET tumors. Credit: *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.abl4414

Researchers with the Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine and collaborators have shown that immature natural killer (NK) cells are present in patients with triple-negative breast cancer (TNBC) and likely promote, instead of inhibit, disease progression in this cancer type.

Their study, featured March 8 in *Science Translational Medicine*, could help clinicians combat treatment resistance in TNBC, one of the most aggressive breast tumors, by identifying certain NK cells as potential therapeutic targets.

NK cells are generally considered an effective contributor to anti-tumor immune responses. "However, not all NK cells are created equal," said Rumela Chakrabarti, Ph.D., associate professor with Sylvester's Tumor Biology Program and corresponding author of the study. "Immature NK cells were present in tissue samples from patients with triple-negative breast cancer and correlated with a worse prognosis for this patient subset."

Background

Breast cancer is the most frequently diagnosed cancer and remains the

second-leading cause of cancer-related deaths among women in the U.S., with an estimated 275,000-plus new cases reported in 2020.

TNBC, which accounts for 10% to 15% of all breast cancers, is characterized by the lack of estrogen and progesterone receptors, as well as a protein called human epidermal growth factor (HER2). It has higher rates of recurrence and metastases than other breast cancers, and current treatments are often ineffective due to the absence of hormone receptors and HER2 proteins as therapeutic targets.

TNBC most commonly afflicts women under age 40, Black women and those with the BRCA1 gene mutation, according to the American Cancer Society.

Methodology

Chakrabarti and research colleagues were able to identify these rogue NK cells by using powerful RNA sequencing to distinguish cell variation at the single-cell level in patient tissue samples. Traditionally, researchers have used bulk RNA sequencing for this identification, but that method can miss finding these unique NK cells within the tumor microenvironment.

Using an innovative mouse model, the researchers also showed that NK cells promoted, rather than prevented, tumor progression in mice. By depleting these cells or inhibiting Wnt ligand secretion from NK cells to prevent faulty cell signaling that can cause gene disruption and cancer, researchers were able to block this effect in mice. "That suggests that immature NK cells represent a potential therapeutic target for women with TNBC," Chakrabarti said.

Chakrabarti thinks this study could be a "game-changer" for TNBC patients. "Resistance to immunotherapy or chemotherapy poses a big

problem for these patients, as few of them respond favorably to current treatments," she explained. "Finding better drug targets is of paramount importance to improve survival rates."

This study may pave the way to that goal. "Blocking immature NK cells sensitized tumors to chemotherapy in combination with immunotherapy in our mouse models," Chakrabarti said, "opening new avenues for effective treatment."

Chakrabarti and colleagues are focusing on how rogue NK cells are created within the tumor microenvironment of aggressive TNBC and their interaction with other immune cells. Their lab also is examining use of the FDA-approved drug LGK-974 to sensitize TNBC tumor cells to chemotherapy and immunotherapy, potentially leading to new and better therapies.

More information: Gatha Thacker et al, Immature natural killer cells promote progression of triple-negative breast cancer, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.abl4414

Provided by Sylvester Comprehensive Cancer Center

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